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Predicting hand function after hemidisconnection: a study on 102 patients

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Abstract

Hemidisconnections (i.e., hemispherectomies or hemispherotomies) invariably lead to contralateral hemiparesis. Many patients with a pre-existing hemiparesis, however, experience no deterioration in motor functions, and some can still grasp with their paretic hand after hemidisconnection. The scope of our study was to predict this phenomenon.

Hypothesising that preserved contralateral grasping ability after hemidisconnection can only occur in patients controlling their paretic hands via ipsilateral corticospinal projections already in the preoperative situation, we analysed the asymmetries of the brainstem (by manual MRI volumetry) and of the structural connectivity of the corticospinal tracts within the brainstem (by MRI diffusion tractography), assuming that marked hypoplasia or Wallerian degeneration on the lesioned side in patients who can grasp with their paretic hands indicate ipsilateral control.

102 patients who underwent hemidisconnections between 0.8 and 36 years of age were included. Before the operation, contralateral hand function was normal in 3/102 patients, 47/102 patients showed hemiparetic grasping ability and 52/102 patients could not grasp with their paretic hands. After hemidisconnection, 20/102 patients showed a preserved grasping ability, and 5/102 patients began to grasp with their paretic hands only after the operation. All these 25 patients suffered from pre- or perinatal brain lesions. 30/102 patients lost their grasping ability. This group included all seven patients with a postneonatally acquired or progressive brain lesion who could grasp before the operation, and also all 3 patients with a preoperatively normal hand function. The remaining 52/102 patients were unable to grasp pre- and postoperatively.

On MRI, the patients with preserved grasping showed significantly more asymmetric brainstem volumes than the patients who lost their grasping ability. Similarly, these patients showed striking asymmetries in the structural connectivity of the corticospinal tracts.

In summary, normal preoperative hand function and a postneonatally acquired or progressive lesion predict a loss of grasping ability after hemidisconnection. A postoperatively preserved grasping ability is possible in hemiparetic patients with pre- or perinatal lesions, and this is highly likely when the brainstem is asymmetric and especially when the structural connectivity of the corticospinal tracts within the brainstem is asymmetric.

Keywords

Hemidisconnection; ipsilateral (re-)organisation; congenital hemiparesis; diffusion-weighted MRI tractography

Abbreviations

AHA = assisting hand assessment

TMS = transcranial magnetic stimulation

Introduction

Hemidisconnection, i.e. the complete surgical disconnection of one cerebral hemisphere, is an important treatment option for pharmaco-refractory hemispheric epilepsies (Vining *et al.*, 1997; Cross, 2002; Devlin *et al.*, 2003; Jonas *et al.*, 2004; González-Martínez *et al.*, 2005; Shimizu, 2005; van Empelen *et al.*, 2005; Delalande *et al.*, 2007; Scavarda *et al.*, 2009; Marras *et al.*, 2010; Dagar *et al.*, 2011; Schramm *et al.*, 2012; Thomas *et al.*, 2012; Dorfmueller and Delalande, 2013). This procedure is mostly applied in children, where it accounts for approximately 16% of all performed epilepsy surgeries (Harvey *et al.*, 2008). The success rate is high, with 65-90% (Graveline *et al.*, 1999; Daniel *et al.*, 2001; Cross, 2002; Villemure and Daniel, 2006; Griessenauer *et al.*, 2015) of all operated patients becoming seizure-free.

The “side effect” of hemidisconnection, in addition to the general risks implied by major brain surgery, is that all brain functions which were located in the epileptic hemisphere are lost. Therefore, hemidisconnection invariably leads to contralateral hemiparesis, and this hemiparesis is often so severe that all active hand functions are permanently lost. A subgroup of hemidisconnected patients can, however, still use the contralateral hand at least for active grasping – and this ability makes an important difference for the many bimanual activities of daily living. Therefore, the prediction of contralateral hand function is an important step in the preoperative work-up of these children. Although several articles have dealt with this topic already (Graveline *et al.*, 1999; Rutten *et al.*, 2002; Govindan *et al.*, 2010; Zsoter *et al.*, 2012; Moosa *et al.*, 2013; van der Kolk *et al.*, 2013; Jeong *et al.*, 2014), prediction in an individual patient still remains challenging. To improve the accuracy of this prediction was the scope of the present study.

In previous reports, all patients with preserved active hand function after hemidisconnection had, to our knowledge, suffered from a pre-existing “congenital hemiparesis”, i.e. hemiparesis caused by a pre- or perinatally acquired brain lesion (Damásio *et al.*, 1975; Kaas, 1991; Chugani *et al.*, 1996;; Holthausen and Strobl, 1999; Rutten *et al.*, 2002; Villemure and Daniel, 2006). In contrast, hand function was lost in patients with a hemiparesis acquired later in life (Gardner *et al.*, 1955; de Bode *et al.*, 2005).

The explanation why only children with early acquired hemiparesis can show preserved residual hand function after hemidisconnection might be quite simple: Unilateral lesions to the motor system acquired early in life can lead to the preservation of normally transient ipsilateral

corticospinal projections, thus allowing the contralesional hemisphere to exert motor control over the paretic hand (Staudt *et al.*, 2002; Eyre, 2003; Staudt, Gerloff, *et al.*, 2004; Krägeloh-Mann and Cans, 2009). This peculiar type of “ipsilateral corticospinal (re-) organisation” is no longer available when a lesion is acquired “late”, probably after the age of two years (Maegaki *et al.*, 1997). We therefore hypothesised that preserved grasping ability after hemidisconnection can only occur in patients controlling their paretic hands via ipsilateral corticospinal projections.

In clinical practice, two approaches can be used to look at the integrity of preserved crossed corticospinal projections on the one hand, and for the presence of ipsilateral corticospinal projections on the other hand: focal transcranial magnetic stimulation (TMS) and analysis of structural MRI.

As for TMS, previous reports on the prediction of hand function after hemidisconnection have already suggested a high prognostic significance to the detection of fast-conducting ipsilateral corticospinal projections to the paretic hand (Rutten *et al.*, 2002; Zsoter *et al.*, 2012). TMS can, however, not be performed in most candidates for hemidisconnections due to young age, lack of cooperation and high stimulation thresholds caused by antiepileptic medication.

MRI, in contrast, can be obtained in all patients, using sedation or anesthesia if necessary. Here, extensive destructive unilateral brain lesions suggesting disruption of the corticospinal tract in a grasping patient would implicitly indicate ipsilateral corticospinal control of the paretic hand. Conversely, MRI evidence for intact crossed corticospinal projections in the lesioned hemisphere would make preservation of contralateral grasping ability after hemidisconnection less likely. Based on this theory, van der Kolk *et al.* (van der Kolk *et al.*, 2013) correctly predicted preservation of grasping after hemidisconnection in two patients by anatomical analysis at four different levels (handknob region, subcortical white matter, posterior limb of the internal capsule and brainstem). We hypothesised, however, that an analysis of brainstem asymmetry alone would be equally significant, as Wallerian degeneration after supratentorial lesions affecting the corticospinal tract is reflected in abnormal asymmetry of the brainstem (Staudt *et al.*, 2000; Duque *et al.*, 2003). While brainstem asymmetry in adult stroke patients correlates with motor impairment (Sonoda *et al.*, 1992; Chugani *et al.*, 1996), we expected it in grasping patients with congenital hemiparesis to indicate motor (re-)organisation involving

ipsilateral corticospinal projections- and, thus, to predict preserved grasping after hemidisconnection.

Further to a volumetric assessment of brainstem asymmetry, we analysed structural connectivity specifically in the corticospinal tract using diffusion-weighted MRI tractography. This might allow a more specific quantification of corticospinal tract damage, which should be more directly related to hand function.

Relying on our central assumption that only patients with ipsilateral corticospinal projections will be able to grasp with their paretic hand after hemidisconnection, we translated this assumption into three more concise hypotheses:

H1: Patients with normal preoperative hand function will not be able to grasp postoperatively (since normal hand function is generally not possible using ipsilateral corticospinal projections (Staudt, Gerloff, *et al.*, 2004)).

H2: Preserved contralateral grasping will only occur in patients with pre- or perinatally acquired brain lesions.

H3: Asymmetry of the brainstem and, more specifically, asymmetry of the corticospinal tract within the brainstem will predict preserved grasping ability.

Materials and methods

This study was based on data of 110 patients (41 female) who underwent hemidisconnections at the epilepsy centre in Vogtareuth, Germany, in the period 1999-2014. Age at surgery ranged from 10 months to 36 years (median 5.5 years).

Two different types of hemidisconnections were performed: Until 2007, a periinsular functional hemispherectomy (Kestle *et al.*, 2000; Villemure and Daniel, 2006) (n=58) and thereafter, a vertical parasagittal hemispherotomy (Delalande *et al.*, 2007; Dorfer *et al.*, 2013) (n=57, including 5 patients who had a foregone periinsular functional hemispherectomy) were performed. The mortality rate was 2/58 for the periinsular functional hemispherectomy (2 days and 22 months after the operation) and 0/57 for the vertical parasagittal hemispherotomy.

8/110 patients had to be excluded from the study: three due to possibly motor relevant postoperative complications in the contralesional hemisphere, two because of death and three because of insufficient documentation. The clinical and MRI data of the remaining 102 patients are summarised in Table 1.

16/102 patients underwent epilepsy surgeries prior to the hemidisconnections. In order to exclude interference of these operations with the purpose of our study, we included only data from the time before the first operation in our analyses (hand function and MRI in 8 patients; hand function only in 4 patients). Only when we could exclude an effect of these prior operations on hand function (i.e., no anatomical interference with the sensorimotor system, e.g. temporo-parieto-occipital resections or callosotomies, and unchanged postoperative hand function), we included also hand function and MRI data acquired from the time after these prior operations, but before the hemidisconnections (4 patients). 17/102 patients had to undergo secondary hemispheric surgery due to incomplete disconnection. Of these, we included only hand function and MRI data from the time before the first operation and after the last operation. Postsurgical seizure outcome was classified according to Engel (Engel, 1993), describing the status at the last follow-up examination, minimum 6 months after the last operation. Engel I was achieved in 77/102 patients.

77/102 patients had pre- or perinatal lesions (12 with hemimegalencephalies, 20 with focal cortical dysplasias, 16 with polymicrogyrias, 10 with periventricular lesions due to periventricular haemorrhagic infarctions or periventricular leukomalacia, 19 with

corticosubcortical lesions due to thromboembolic infarctions, including one patient with neonatal traumatic brain injury at the age of 2 weeks resulting in a unilateral ischaemic lesion; Table 1). 24/102 patients had postneonatally acquired lesions (i.e. after the age of 4 weeks, e.g. stroke, hemiconvulsion-hemiplegia epilepsy syndrome or traumatic brain injury, n=13) or progressive lesions (such as Rasmussen's Encephalitis). 1/102 patient was not reliably classifiable. Allocation to these subgroups was based on MRI analysis and histopathological examination of resected tissue.

Clinical data were acquired by a retrospective analysis of hospital charts. In all 102 patients, pre- and postoperative hand function could be categorised either as “normal”, as “hemiparetic with grasping ability” or as “hemiparetic without grasping ability”. In a subgroup of 15 patients, bimanual performance was formally tested in the pre- and postoperative periods, using the Assisting Hand Assessment (AHA) (Krumlinde-Sundholm *et al.*, 2007). The AHA is a well-established, standardised assessment tool to measure how effectively hemiparetic children and adolescents use their paretic hand in bimanual activities. It results in linearly scaled “AHA units” (0 – 100), with higher numbers indicating higher ability (Krumlinde-Sundholm *et al.*, 2007). Differences of 5 units or more between assessments are considered clinically significant changes) (Krumlinde-Sundholm *et al.*, 2012). All AHAs were performed by AHA-certified occupational therapists from the paediatric neurorehabilitation center in Vogtareuth.

Pre-operative MRI data acquisition had been performed on three different 1.5-T MR scanners involving different scanning protocols. T1-weighted three-dimensional datasets were available in 77 patients, axial T1-weighted datasets in 12 patients and diffusion-weighted MRI datasets in 40 patients (Table 1).

A volumetric analysis of brainstem asymmetry (on axial T1-weighted MRI) was performed by manually delineating the cross-sectional area of the left and right brainstem from the level of the cerebral peduncles down to the level of the medulla oblongata on contiguous axial slices of the T1-weighted anatomical MRI (Fig. 1), using easily identifiable anatomical landmarks such as the mammillary bodies and the middle cerebellar peduncles to ensure inter-subject comparability. This resulted in the volumes of the left and right brainstem.

The structural connectivity of the left and right corticospinal tract within the brainstem was determined using probabilistic MRI diffusion tractography. Guided by the directionally-

encoded colour map (Pajevic and Pierpaoli, 2000), a manual seed region was defined in the anterior part of the cerebral peduncle and a manual inclusion region in the anterior part of the medulla oblongata within the same brainstem section as defined by brainstem volumetry (Fig. 1). Tractography analysis and image processing were carried out using the MRtrix3 package (J-D Tournier, Brain Research Institute, Melbourne, Australia, <https://github.com/MRtrix3/mrtrix3>) and FSL (www.fmrib.ox.ac.uk/fsl), with default parameters. Due to the high amount of crossing fibres in the brainstem (Habas and Cabanis, 2007; Jeurissen *et al.*, 2011) and the low spatial and angular resolution of the diffusion-weighted MRI we had available, we used constrained spherical deconvolution (Tournier *et al.*, 2004; Anderson, 2005) with Rician bias correction and neighbourhood smoothness constraints (Tournier, 2007) as an advanced diffusion MRI analysis approach. Constrained spherical deconvolution can resolve individual fibre bundles within each voxel, estimating the fibre orientation distribution along the pathway of interest. Image intensity normalisation (to make amplitudes of fibre orientation distribution comparable across subjects) was done using the signal of the median $b=0$ image within a brain mask of the diffusion-weighted MRI datasets. After reconstructing the corticospinal tract, all tract-specific fibre orientation distribution integrals within the voxels belonging to this pathway of interest were added and divided by the pathway length resulting in the “apparent fibre density” (Raffelt *et al.*, 2012; Jeurissen *et al.*, 2014) as a tract-specific and biologically interpretable estimate of structural connectivity of the corticospinal tract. This was done using the “afdconnectivity” command in MRtrix3.

Finally, asymmetry indices $[(\text{contralesional side} - \text{lesional side})/(\text{contralesional side} + \text{lesional side})]$ were calculated for the T1-based brainstem volumes and for the tractography-based structural connectivity of the corticospinal tract segment (Fig. 1).

In order to transfer the tractography-based corticospinal tract analysis into clinically applicable practice, a **pragmatic visual analysis** of directionally-encoded colour fractional anisotropy maps was conducted. These maps are easily available during clinical routine, since most MR scanners provide these images automatically when diffusion-weighted imaging is acquired. Visual inspection of axial slices of the brainstem from the level of the cerebral peduncles down to the upper border of the medulla oblongata was performed. An experienced examiner (MS), blinded to all clinical information and to the supratentorial MRI, categorised the asymmetry of the corticospinal tract on these slices as follows (Fig. 5):

Group A: **No consistent asymmetry** of the corticospinal tracts- the lesional side cannot safely be determined.

Group B: **Some asymmetry**- the lesional side can safely be determined as smaller, however the corticospinal tract of the lesional side is clearly visible on all slices.

Group C: **Marked asymmetry**- the corticospinal tract on the lesional side becomes regionally so thin that it is not clearly visible on one or more slices.

The same dataset was assessed one year later, again by the initial rater MS and independently also by a second rater (TP), so that intra-rater and inter-rater reliability could be assessed.

Transcranial magnetic stimulation (TMS) had been carried out in 14 patients in the course of the preoperative evaluation as described in Staudt et al. (Staudt, Gerloff, *et al.*, 2004). In brief, both hemispheres were searched systematically for areas from where motor-evoked potentials could be elicited (recorded via surface electrodes from first interosseus dorsal muscles of both hands simultaneously), using a focal 2x 70 mm figure-of-eight coil and a MagStim 200 stimulator. Due to the often low cooperation of our patients, in most cases we did not assess motor thresholds and latencies at a pre-defined level of stimulation; instead, we increased the stimulation intensity rather rapidly, until motor evoked potentials could reliably be elicited, and measured the latencies at this intensity of stimulation (Staudt, 2010). The examination always started with the contra-lesional hemisphere, and the stimulation intensity was increased until bilateral motor evoked potentials were elicited, or until 100% of stimulator output was reached. We then stimulated the lesioned hemisphere, again increasing the stimulation intensity until motor evoked potentials were elicited, or until 100% of the maximum stimulator output was reached.

Statistical analysis

Differences in asymmetry indices between patient groups were tested for significance using the Mann Whitney U test, with $p < 0.05$ as significance level. Intra- and interrater reliabilities were described with Cohen's Kappa. Spearman rank analysis was applied to test for correlations between asymmetry indices and pragmatic visual analysis.

Results

Before the operation, hand function was normal in 3/102 patients, 47/102 patients showed hemiparetic grasping ability and 52/102 patients could not grasp with their paretic hand.

Of the three patients with **normal preoperative hand function**, all (3/3) lost their contralateral grasping ability. These 3 patients suffered from hemispheric cortical dysplasia.

Of the 47 hemiparetic patients **who could grasp before the operation**, 20/47 patients showed a preserved grasping ability after hemidisconnection. All 20 patients had a pre- or perinatal brain lesion. The other 27 patients in this group lost their grasping ability in the course of the operation. This subgroup included all seven patients with a postneonally acquired or progressive lesion (1/7 postinflammatory lesion, 2/7 Sturge-Weber syndrome and 4/7 Rasmussen's encephalites) who could grasp with their paretic hand preoperatively.

Of the 52 patients **without grasping ability** before the operation, five patients acquired a grasping ability after the operation. Again, all five patients suffered from pre- or perinatal brain lesions. The other 47 patients in this group (no grasping pre- and postoperatively) showed all types of underlying pathologies and timing periods.

Therefore, in all groups, postoperative grasping was only observed in patients with pre- or perinatally acquired brain lesions (Table 1).

In the 50 patients **who could grasp before the operation**, asymmetry indices for the brainstem volume as well as for the structural connectivity of the corticospinal tract were significantly higher in patients with preserved grasping than in patients who lost their grasping ability after hemidisconnection (for both: Mann Whitney U, $p < 0.001$; see Fig. 2). But whereas considerable overlap was observed for the asymmetry of the brainstem volumes (Fig. 2A), the asymmetry of the structural connectivity of the corticospinal tract showed a clear separation (Fig. 2B): All patients with an asymmetry index of more than 0.4 could still grasp after the operation, (positive predictive value of 100%), whereas all patients with an asymmetry index of less than 0.2 lost their grasping ability after the operation (negative predictive value of 100%). This superior discriminatory power of corticospinal tract asymmetry was still evident when the analysis was confined to the 19 patients in whom both T1-weighted images and diffusion MRI were available: In contrast to the clear separation for the structural connectivity data (yielding

positive and negative predictive values of 100%), an overlap was still present for the brainstem asymmetry data, with a positive predictive value of 80% and a negative predictive value of 87% when a cut-off of 0.03 was applied.

Fig. 3 gives examples of anatomical correlates of asymmetry versus symmetry associated with preserved versus lost grasping ability of the paretic hand in two pairs of patients with polymicrogyrias and periventricular lesions. Fig. 6 (supplementary online material) shows marked differences in asymmetry of the corticospinal tracts at brainstem level in three patients with extensive hemispheric lesions where wholebrain tractography demonstrated rather symmetrically appearing corticospinal tracts at supratentorial level. Note that, for reasons of illustrational uniformity, some MRI images were flipped horizontally so that the lesioned hemisphere could always be depicted as the right hemisphere. Denotation of MRI images was ordered chronologically across all figures (#1- #8) so that corresponding illustrations of the same patient could be recognised.

The **pragmatic visual analysis** of directionally-encoded colour fractional anisotropy maps correlated significantly with the asymmetry of the structural connectivity of the corticospinal tract (Spearman rank; $r_s = 0.744$, $p < 0.001$). Furthermore, this approach also showed a surprisingly good prediction: In group A (no asymmetry; $n = 17$) and B (some asymmetry; $n = 11$), all 14 patients who could grasp preoperatively lost this ability. In contrast, in group C (marked asymmetry; $n = 12$), all five patients who could grasp preoperatively preserved this ability. Therefore, the positive and negative predictive values of this assessment were also 100%. Repeated assessments of the same MRI datasets (confined to A & B = “high risk” versus C = “low risk”) confirmed high values both for intra-rater reliability (Cohen's Kappa = 0.94) and for inter-rater reliability (Cohen's Kappa = 0.79).

Assisting Hand Assessments (AHA) of paretic hand use during bimanual activities in the pre- and postoperative period showed quite variable results (Fig. 4). Of the four patients with **preserved grasping ability** (green lines in Fig. 4), one improved significantly ($35 \rightarrow 47$ AHA units), one remained unchanged ($41 \rightarrow 40$ AHA units), one deteriorated initially but returned to the pre-operative level 12 months later ($58 \rightarrow 54 \rightarrow 58$ AHA units), and one showed a marked deterioration initially with incomplete recovery 14 months later ($66 \rightarrow 48 \rightarrow 57$ AHA units). Of the five patients who **lost their grasping ability** (red lines in Fig. 4), the four patients with high preoperative values showed a dramatic deterioration, whereas the girl with poor bimanual

performance despite grasping ability in the preoperative period showed only minor changes (16 → 22 AHA units) although her grasping ability was lost. **Diffusion-weighted MRI tractography** was available in 10 of the 16 patients who underwent pre- and postoperative AHAs. The prediction of post-operative bimanual performance based on corticospinal tract asymmetry was excellent for the patients with good paretic hand use ($AHA \geq 50$): The three patients who lost their grasping ability and dropped to AHA values of 25 or less showed rather symmetric corticospinal tracts (asymmetry indices of 0.00, 0.03 and 0.05; red boxes in Fig. 4), whereas the two patients with preserved grasping ability and only minor deterioration had asymmetric corticospinal tracts (asymmetry indices 0.55 and 0.51; green boxes in Fig. 4).

Transcranial magnetic stimulation (TMS) of the contra-lesional hemisphere elicited motor evoked potentials in both hands in all 14 patients studied (Table 1). As expected, latencies were always short for the (contralateral) non-paretic hand (13 – 20 ms). In the (ipsilateral) paretic hand, latencies were similarly short (differences within ± 1 ms to the non-paretic hand) in 10/14 patients. These patients showed a preserved grasping ability postoperatively ($n = 9$), or could not grasp pre- and postoperatively ($n = 1$). Somewhat longer latencies in the paretic hands were observed in two patients, one who lost his grasping ability postoperatively (2 - 3 ms difference) and one who acquired her grasping ability only after the operation (3 - 7 ms difference). Due to the poor cooperation of these patients, however, these exceptions might well be arteficial, and should therefore not be over-interpreted. Finally, in two patients with preserved grasping ability, motor evoked potentials in the paretic hand were clearly visible, but the latency could not reliably be determined.

Discussion

Investigating clinical data and MRI in 102 patients who underwent hemidisconnections, several predictive factors for postoperative grasping ability could be elaborated, thereby confirming all three postulated hypotheses (H1-3). This corroborates our central assumption that grasping of the paretic hand following hemidisconnection is conveyed via ipsilateral corticospinal projections.

H1: Patients with normal preoperative hand function will not be able to grasp postoperatively.

In the rare situation of a hemidisconnection despite a **preoperatively normal hand function**, i.e. in the absence of a hemiparesis, the complete loss of contralateral grasping must be expected. All three patients in our cohort showed this course. Also, this appears likely since a normal motor hand function has been described to rely on classical crossed corticospinal projections of neural hand control (Staudt *et al.*, 2002; Eyre, 2003).

H2: Preserved contralateral grasping ability will only occur in patients with pre- or perinatal brain lesions

In our series, preserved or acquired postoperative grasping ability occurred only in patients with pre- and perinatal brain lesions, whereas all seven patients with a postneonatal or progressive lesion who could grasp preoperatively lost this ability.

These observations are in line with previous, mostly casuistic reports of preserved grasping ability after hemidisconnection in patients with hemiparesis due to pre- or perinatally acquired lesions (Damásio *et al.*, 1975; Kaas, 1991; Chugani *et al.*, 1996; Holthausen and Strobl, 1999; Rutten *et al.*, 2002; Villemure and Daniel, 2006). On the other hand, our observations of a lost grasping ability in patients with postneonatally acquired or progressive lesions are in accordance with findings of de Bode *et al.* (de Bode *et al.*, 2005) where all patients with Rasmussen's encephalites had no useful hand ability after hemispherotomy and of Gardner *et al.* (Gardner *et al.*, 1955) where all patients with hemispherectomies as a treatment for hemispheric gliomas diagnosed as adults had lost all useful grasping ability of the paretic hand (Gardner *et al.*, 1955).

We do not know, however, whether the neonatal period really is the last time until which efficient ipsilateral control of a paretic hand can develop. In our data, only three patients had

lesions acquired during the first year of life – and all three lost their grasping ability. On the other hand, fast-conducting, ipsilateral corticospinal projections have been detected in healthy children until the age of 18 months (Eyre *et al.*, 2001) and in hemiparetic children with lesion onsets up to a maximum age of 2 years (Maegaki *et al.*, 1997), after TMS of the contralesional hemisphere. Therefore, we cannot exclude that, in rare cases, preserved postoperative grasping could also occur in patients with lesions acquired during the first months of life. Due to the paucity of data in this age range both in our cohort and in the literature, this question remains unanswered.

In the subgroup of patients with pre- and perinatal lesions, however, 20 patients also lost their grasping ability after hemidisconnection. This underlines that crossed corticospinal organisation is equally possible in pre- and perinatal lesions (Staudt *et al.*, 2004) which underlines the complexity of interacting factors resulting in ipsilateral (re-)organisation. Here, the very broad morphological spectrum of malformations of cortical development (Holthausen and Strobl, 1999; Vandermeeren *et al.*, 2002; Burneo *et al.*, 2004; Staudt *et al.*, 2004) should be considered, concerning factors such as specific timing, localisation, size and functional integrity of a lesion (Chugani *et al.*, 1996; Bernasconi *et al.*, 2000; Staudt *et al.*, 2002).

Especially in the view of this underlying complexity, the simple analysis of brainstem asymmetry proved to be of valuable and clinically relevant predictive value.

H3: Asymmetry of the brainstem and, more specifically, of the corticospinal tract within the brainstem will predict preserved grasping ability.

Asymmetry of the brainstem and asymmetry of the structural connectivity of the corticospinal tract were both significantly associated with a postoperatively preserved grasping ability. Furthermore, as hypothesised, the specific delineation of the corticospinal tract with regard to asymmetry showed a more reliable prediction than the more general approach of brainstem volumetry (Fig. 2). This was still evident when comparing brainstem asymmetry with corticospinal tract asymmetry within the subgroup of preoperatively grasping patients who had received both T1-weighted MRI and diffusion-weighted MRI tractography.

The advantage of a tractography-based evaluation in patients with motor impairment has already been described elsewhere: Son *et al.* (Son *et al.*, 2007) detected focal lesions of the

corticospinal tract in patients with cerebral palsy where conventional MRI showed no abnormalities. Altered diffusion parameters in the corticospinal tract have been associated with Wallerian degeneration following ischaemic arterial infarctions in paediatric and adult patients (Pierpaoli *et al.*, 2001; Khong *et al.*, 2004; Glenn *et al.*, 2007) which correlated with functional impairment, regardless of the aetiology of motor dysfunction. While Govindan *et al.* (Govindan *et al.*, 2010) used diffusion tensor tractography for visual analysis of the corticospinal tract in the preoperative assessment in a single patient, we quantitatively measured asymmetry of the structural connectivity of the corticospinal tract with regard to its predictive value for the presence of ipsilateral corticospinal projections in a group of 40 patients.

The here presented optimised algorithm of calculating the structural connectivity of the corticospinal tract (including constrained spherical deconvolution and apparent fibre density), however, is time-consuming and requires special expertise. We have therefore tried a much simpler approach of visually analysing the asymmetry of the corticospinal tract on directionally-encoded fractional anisotropy maps, which most scanners automatically provide when diffusion-weighted imaging is performed. This pragmatic visual analysis showed an equally high positive and negative predictive value (both 100%), and also high intra-rater and inter-rater reliabilities. Therefore, this simple visual analysis holds promise to become a valuable tool for clinical routine, although the results still must be confirmed in larger and, ideally, prospective studies.

Notably, 5 patients **acquired a grasping ability** of their paretic hand only in the postoperative course, all displaying pre- and perinatal brain lesions. The age at operation in this subgroup ranged from 2 years to 13 years. Therefore, maturational factors as explanation for this phenomenon seem unlikely. Rather, a negative effect of the epileptic disorder on motor function in the contra-lesional hemisphere appears probable which was stopped by hemidisconnection, thereby enabling functional access to preexisting motor networks in the contralesional hemisphere, as suggested by Pascoal *et al.* (Pascoal *et al.*, 2013). This hypothesis is corroborated by the fact that 4/5 patients had early onset of epileptic seizures (within the first months of life). Predictive factors differentiating these five from the other 29 patients with pre- and perinatal brain lesions who had no grasping ability of the paretic hand pre- and postoperatively could not be derived. Altogether, the phenomenon of a postoperatively newly acquired grasping ability of the paretic hand is rare and difficult to predict.

Assisting Hand Assessment (AHA) in a subgroup of 15 patients showed that patients can experience improvements as well as deteriorations of bimanual performance after hemidisconnection even when the simple hand function of **grasping is preserved**. The patient who improved gives another example of a negative impact of the epilepsy on bimanual performance in the preoperative period, which was stopped by the hemidisconnection, so that paretic hand use during bimanual performance increased. Our observation of a marked deterioration despite preserved grasping in a patient with hemispheric polymicrogyria (66 → 48 AHA units) indicates that, in this girl, the epileptic hemisphere apparently had also harboured hand functions. This patient had shown good somatosensory functions in the paretic hand preoperatively (4 mm two-point-discrimination at paretic thumb), but a marked somatosensory deficit after the operation (> 3 cm two-point-discrimination). This suggests that the primary somatosensory representation of the paretic hand had been located in the polymicrogyric hemisphere (as reported previously for patients with hemispheric polymicrogyrias, Zsoter et al). Therefore, her deterioration in paretic hand use could be related to the post-operative loss of somatosensory functions. Interestingly, one year after the operation, bimanual performance had ameliorated again (→ 57 units), probably reflecting adaptation of hand motor control in the remaining hemisphere to the new situation – although her two-point discrimination was still low (> 3 cm). The hypothesis of a loss of somatosensory functions in the epileptic hemisphere as the reason for deterioration in paretic hand use is further corroborated by the second patient with well-preserved bimanual performance (58 → 54 → 58 AHA units). In contrast to the above-mentioned girl with the polymicrogyria, this girl with a perinatally acquired cortico-subcortical infarct had had poor somatosensory functions in the paretic hand already preoperatively (> 3 cm two-point-discrimination at paretic thumb), so that the hemidisconnection could not lead to a functionally relevant loss here. Accordingly, her post-operative AHA was only slightly smaller, and returned to the preoperative value after one year. But although suggestive, more observations are needed before drawing conclusions on the predictive value of somatosensory functions concerning paretic hand use following hemidisconnections. In the five patients who had **lost their grasping ability**, postoperative bimanual performance remained always poor (below 30 AHA units). This was a dramatic loss for the four patients with a good bimanual performance in the preoperative phase, since, despite all neurorehabilitative efforts, none of these patients were able to reach AHA scores of more than 24 units in the long run. The girl with poor bimanual performance despite grasping ability in the preoperative phase showed only minor changes in bimanual performance – although she had lost her ability to grasp. Therefore, the prediction of a loss of grasping ability in patients

with poor paretic hand use already in the pre-operative period does not necessarily also imply a deterioration in bimanual performance.

Transcranial magnetic stimulation demonstrating only ipsilateral corticospinal projections to the paretic hand correctly predicted postoperatively preserved grasping ability in 12/13 patients. This observation is in line with other reports (Britton *et al.*, 1991; Staudt *et al.*, 2002; Rutten *et al.*, 2002; Zsoter *et al.*, 2012) - although the prediction was not 100% accurate in our patient sample. Due to the small number of patients in our series (a consequence of the cooperational requirements of this technique) and the fact that no subjects with the classical contralateral projection pattern were included (who would have provided counter-examples), these results must be considered preliminary and indicative but require further confirmation.

Admittedly, this study has several **shortcomings**: Our clinical data was based on a retrospective analysis of hospital charts, only resulting in a broad classification of motor hand function, and the more detailed analysis of paretic hand use (the AHA) was only available in 16 patients. Further, diffusion-weighted MRI datasets were only available in a subset of 40 patients. Our findings, especially those regarding the predictive value of corticospinal tract connectivity and of the pragmatic visual analysis of fractional anisotropy maps, therefore need further validation in a larger patient group.

In conclusion, the following **“rules” for the prediction of grasping ability following hemidisconnection** could be elaborated:

- When hand function is normal, a complete loss of grasping ability must be expected.
- In patients with postneonatally acquired lesions or with progressive lesions, a complete loss of grasping ability must be expected.
- Marked asymmetry of the brainstem and, more specifically, marked asymmetry of the corticospinal tract within the brainstem, predict preservation of grasping ability in patients who can grasp preoperatively.

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Figure legends

Table 1: Patient characteristics.

Numbers of patients with respect to aetiology, availability of diagnostic procedures and pre- and postoperative grasping ability. Note that postoperative grasping (either preserved or newly acquired) was only observed in patients with pre- and perinatal lesions (above dashed line).

Figure 1: Delineation of the brainstem volume and of the structural connectivity of the corticospinal tracts

Axial and coronal T1-weighted MRI (upper row) as well as three-dimensional illustrations of the corticospinal tracts (in blue) as computed by diffusion-weighted MRI tractography (lower row) for a patient (#1) with a cortico-subcortical postischaemic lesion, a patient (#2) with hemispheric polymicrogyria and a patient (#3) with hemimegalencephaly. Manual delineation of the left and right brainstem sides was performed on axial T1-weighted MRI from the level of the cerebral peduncles down to the medulla oblongata, resulting in the volumes of the two halves; the structural connectivity of the brainstem segments of the corticospinal tracts were determined by probabilistic tractography. For both, an asymmetry index (*) was calculated as $(\text{contralesional side} - \text{lesional side}) / (\text{contralesional side} + \text{lesional side})$. Note the marked asymmetry of the brainstem and of the corticospinal tracts in patients #1 and #2 contrasting with the symmetry in patient #3. Accordingly, grasping was preserved after hemidisconnection in patients #1 and #2, but lost in patient #3.

Figure 2: Asymmetry indices of brainstem volume and structural connectivity of the corticospinal tracts

Asymmetry indices for the brainstem volume (as derived from T1-weighted MRI; Fig. 2A) and for the structural connectivity of the corticospinal tracts (as derived from MRI tractography; Fig. 2B) are depicted for each patient with respect to the pre- and postoperative grasping ability of the paretic hand. Significant differences between groups are indicated with p-values (Mann-Whitney-U). Note the different scaling of the two y-axis due to higher asymmetries of the structural connectivity of the corticospinal tract.

Figure 3: Asymmetry versus symmetry in two pairs of patients with polymicrogyrias and periventricular lesions

Illustration of anatomical supra- and infratentorial asymmetry versus symmetry in two pairs of patients with polymicrogyrias (#2, #4) and periventricular lesions (#5, #6) exhibiting a preserved (#2, #5) versus lost (#4, #6) grasping ability of the paretic hand. For each patient, axial slices of T1-weighted MRI at the level of the handknob region (white arrow), of the internal capsule and of the cerebral peduncles are depicted. T1-weighted MRI enlargements of the brainstem at the level of the cerebral peduncles, pons and medulla oblongata are illustrated, alongside with corresponding track density imaging derived from a wholebrain tractography. Track density imaging are depicted with the directionally-encoding colouring (red = left-right; green = anterior-posterior; blue = cranio-caudal). Note the marked asymmetry of the brainstem and of the corticospinal tracts (red arrows) in the patients with post- operatively preserved grasping ability (#2, #5) contrasting with symmetry of the brainstem and of the corticospinal tracts in patients who lost their grasping ability (#4, #6).

Figure 4: Results of the Assisting Hand Assessment (AHA) in the pre- and postoperative phase.

Individual patients' AHA assessments (open circles = grasping, solid circles = not grasping) are connected with lines (colour codes as in Fig. 2, with green = preserved grasping ability, red = lost grasping ability, grey = no grasping pre- and postoperatively). The asymmetry index of the structural connectivity of the corticospinal tracts (available in 10 patients) is given next to the preoperative AHA (in coloured boxes). Note that, for reasons of readability of the diagram, only the first and the last postoperative AHA score is depicted for each patient. In one patient (16 → 22 AHA units) who underwent two hemidisconnections, the blue line "hemidisconnections" refers to the second operation. For those patients, whose MRI are also illustrated in other figures, the corresponding number is depicted on the left (#2, #1, #7).

Figure 5: Pragmatic visual analysis of directionally-encoded colour maps

Directionally-encoded colour maps of fractional anisotropy (as calculated by the standard software of the MRI scanner, and therefore in lower resolution than for constrained spherical deconvolution-based tractography data) are shown for three representative patients. On these maps, fractional anisotropy is coded by brightness, and direction is coded by colour (red = left-right; green = anterior-posterior; blue = cranio-caudal). In the patient with *no asymmetry (left column)*, no consistent asymmetry is visible, so that, in contrast to the other two patients, the

abnormal side could not be guessed by looking at the brainstem alone. In the patient with *some asymmetry (middle column)*, the corticospinal tract on the abnormal side appears smaller on several images, but the blue signal never disappears (*blue arrows*). Finally, in the patient with *marked asymmetry (right column)*, the blue signal in the position of the corticospinal tract is highly asymmetric in the mesencephalon and the upper pons (*yellow arrows*), and virtually disappears in the lower pons and medulla oblongata (*white arrows*).

Figure 6 (Supplementary online material): Examples of hemispheric brain lesions on T1-weighted images with corresponding wholebrain tractograms

Axial and coronal T1-weighted MRI (upper row) along with the corresponding directionally-encoded colour maps of a wholebrain track density imaging (lower row, red = left-right; green = anterior-posterior; blue = cranio-caudal) are depicted for a patient with hemimegalencephaly (#7), a patient with polymicrogyria (#2) and a patient with hemiconvulsion- hemiplegia-epilepsy (#8) as examples of severe hemispheric pathologies.

While the amount of supratentorial blue fibres at the level of the centrum semiovale seems to be comparable in all three patients (white arrows), the amount of blue fibres at brainstem level, presumably corresponding more specifically to the corticospinal tract, differs strongly: In the patient with hemimegalencephaly (#7) who shows a postoperative loss of paretic grasping function the two corticospinal tracts appear symmetric (yellow arrows). In contrast, in the patient with polymicrogyria (#2) who shows a postoperatively preserved paretic grasping ability the two corticospinal tracts show a marked asymmetry (red arrows). This corresponds to the picture of the patient with hemiconvulsion-hemiplegia-epilepsy (#8), acquired at the age of 2 years, who, however, shows no pre- and postoperative paretic grasping function.

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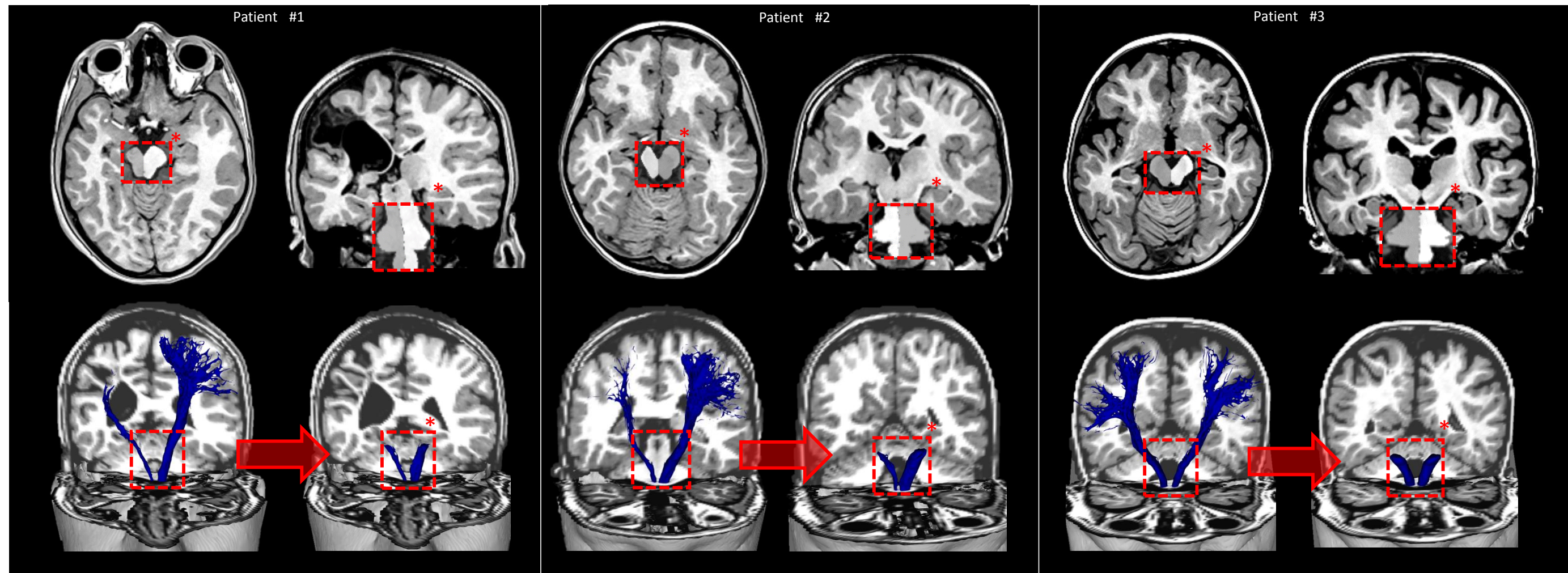
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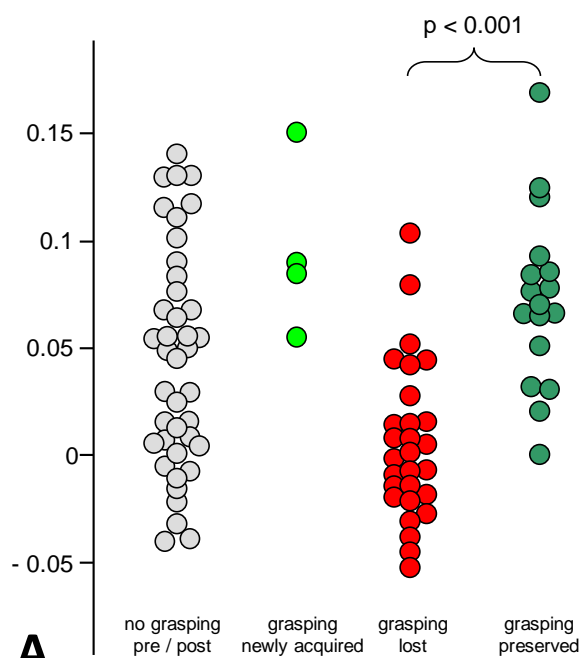
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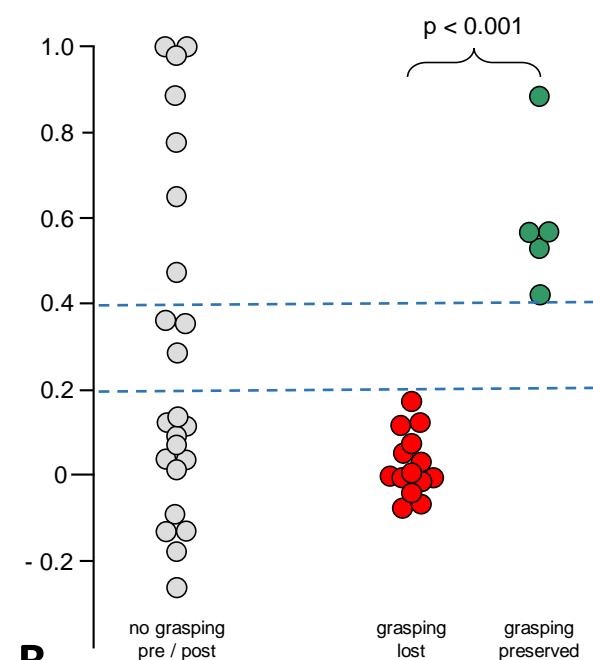
	All					T1					DWI					TMS					AHA				
	N	L	P	A	Σ	N	L	P	A	Σ	N	L	P	A	Σ	N	L	P	A	Σ	N	L	P	A	Σ
Hemimegalencephaly	6	6			12	5	6	0	0	11	3	4			7					0		1			1
Focal Cortical Dysplasia	7	11	1	1	20	4	10	1	0	15	2	6			8					0		1			1
Polymicrogyria	5	2	8	1	16	5	2	7	1	15	4	1	1		6			6	1	7	1		1		2
Periventricular Lesion	4	2	4	0	10	3	2	4	0	9	1	1	1		3			1		1					0
Cortico-subcortical Lesion	7	2	7	3	19	6	2	5	3	16	4		3		7	1	1	4		6	2		3		5
Progressive Lesion	5	6			11	4	5			9	2	2			4					0	1	4			5
Postneonatal Lesion	12	1			13	12	1			13	4				4					0	2				2
Unclassifiable Lesion	1				1	1				1	1				1					0					0
Sum	47	30	20	5	102	40	28	17	4	89	21	14	5	0	40	1	1	11	1	14	6	6	4	0	16



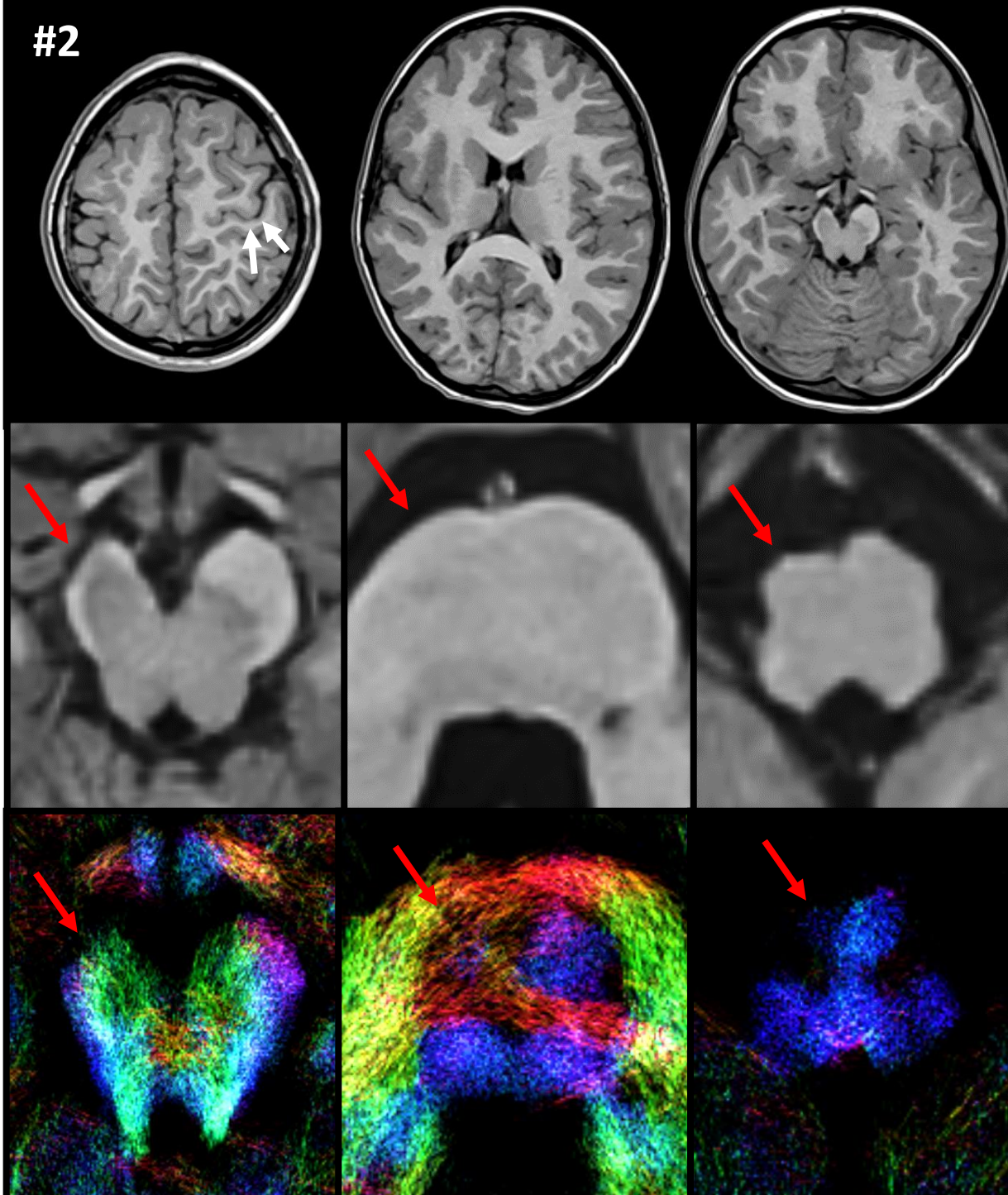
Brainstem Asymmetry Index (n = 89)



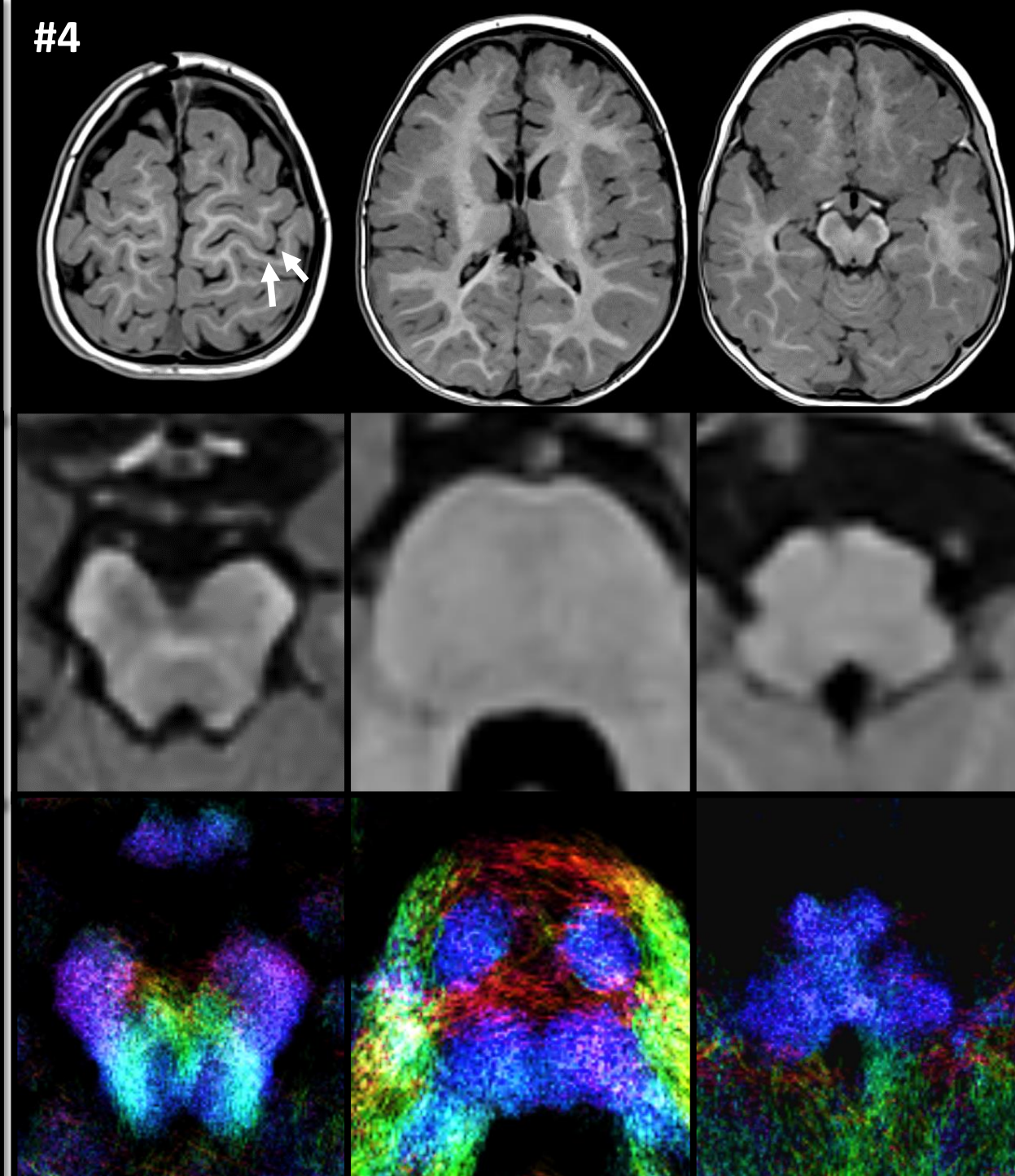
Corticospinal Tract Asymmetry Index (n = 40)



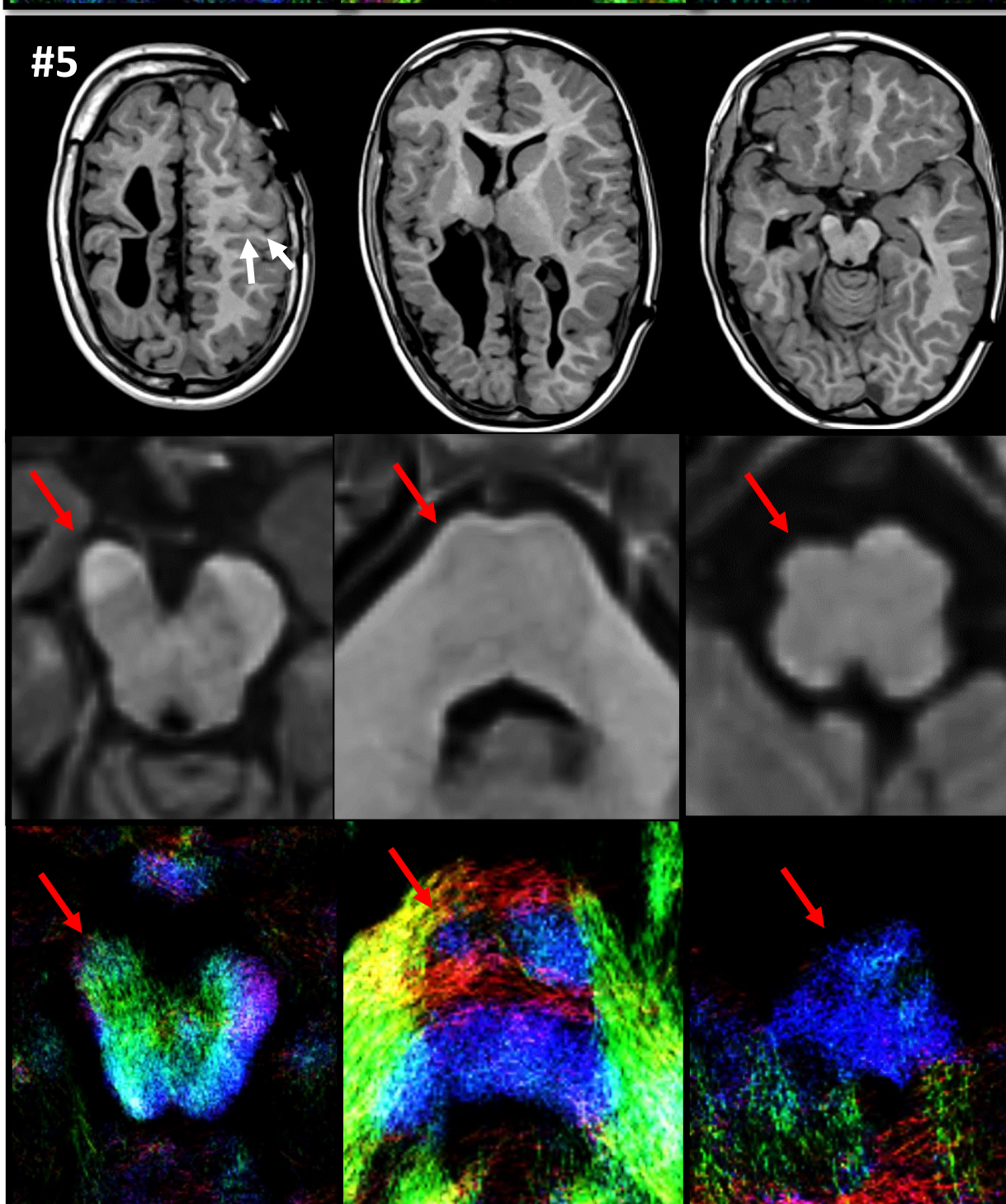
#2



#4



#5



#6

